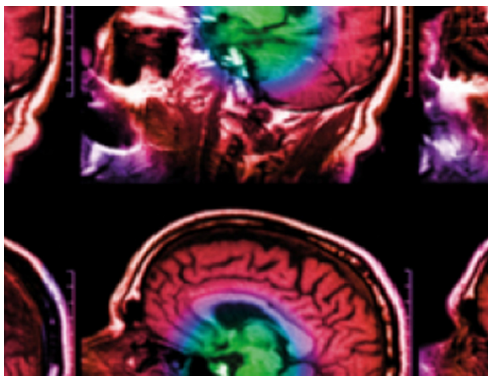


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LETTER

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Spontaneous baroreflex sensitivity: sequence method at rest does not quantify causal interactions but rather determines the heart rate to blood pressure variability ratio

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Abstract

Objective: In order to quantify spontaneous baroreflex sensitivity (BRS) many groups use the sequence method (SME). In this paper we test the hypothesis that SME is quantifying causal interactions of spontaneous BRS at rest rather than, alternatively, being solely dominated by heart rate variability (HRV) and/or systolic blood pressure variability (BPV). **Approach:** Therefore, we retrospectively analyzed 1828 beat-to-beat time series and their corresponding systolic blood pressure during resting conditions. **Main results:** We found a high correlation between short-term HRV and the SME of baroreflex sensitivity of $r = 0.85$ ($p < 0.001$). The correlation is even higher between SME and the root mean square ratio of HRV and BPV ($r = 0.93$, $p < 0.001$). Surrogate analyses revealed that SME is not able to quantify causal relationships between both signals, it cannot differentiate between random and baroreflex driven sequences, and rather determines the HRV-BPV variability ratio. **Significance:** We conclude that SME has a potentially large methodological bias in the characterization of the capacity of the arterial baroreflex during resting conditions.

1. Introduction

The baroreflex exerts a strong influence on the regulation of the cardiovascular system in order to sustain homeostasis. Modelling and quantifying this reflex have a high importance to understand the current state of the cardiovascular system and its behavior. The spontaneous sensitivity of the arterial baroreflex (BRS) is commonly estimated with the sequence method (SME) (Bertinieri *et al* 1985, Rothlisberger *et al* 2003), that supposedly quantifies this reflex directly. To compare its information content, we additionally calculated the short-term heart rate variability (HRV) and systolic blood pressure variability (BPV) which is mostly vagally modulated—including efferent connections from the baroreflex (Task Force 1996, Karemaker and DeBoer 2017). Several previous attempts exist that try to tune parameters in the SME, however, they did not verify if their method actually determines a causal bivariate relationship (Laude *et al* 2009, Silva *et al* 2019). In this letter we test whether SME is actually able to quantify causal interactions between heart rate and blood pressure, and thus estimate spontaneous BRS. Therefore, three surrogate analyses were performed where any actual relationship between blood pressure and heart rate signal was non-existent by construction.

2. Data

To include a broad spectrum of baroreflex regulation, we pooled the data from five different studies in obstetrics, genetics, cardiology and heart surgery (Boyé *et al* 2011, Faber *et al* 2004, Barantke *et al* 2008, Retzlaff *et al* 2009, 2011) (cf. table 1). All patients gave written, informed consent, and all studies were approved by the respective local Ethics Committees. From obstetrics (Faber *et al* 2004) we included 915 measurements of 304 pregnant women, mean age 28.4 ± 5.4 years. There were 398 recordings of healthy

Table 1. Demographic data of all sub-studies (HPD: hypertensive pregnancy disorders, OHD organic heart disease, CAD coronary artery disease, DCM dilated cardiomyopathy, AV: aortic valve MV: mitral valve surgery, SAVR: surgical aortic valve replacement, TAVI: trans-catheter aortic valve implantation).

	Obstetrics	Genetics	Cardiology	Surgery I	Surgery II
<i>n</i> patients	304	367	75	101	58
# measurements	915	367	75	302	169
Age	28.4 ± 5.4	45.0 ± 16.3	70.9 ± 10.1	60.1 ± 6.3	72.2 ± 10.2
Disease	HPD 46.5%	OHD 0%	CAD 53% DCM 8% Other 39%	AV 60% MV 40%	SAVR 59% TAVI 41 %

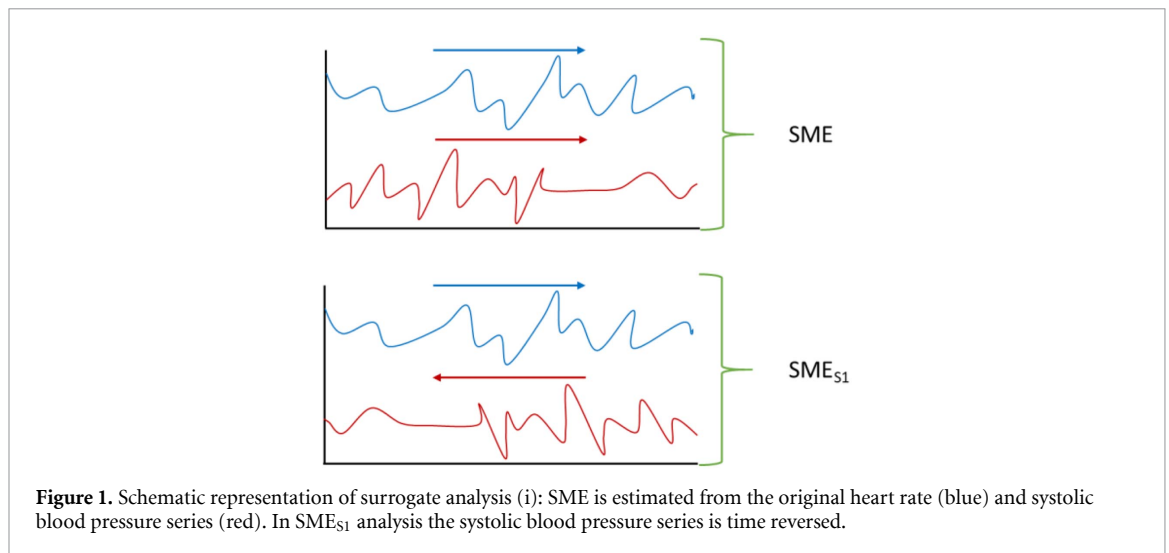
women, 120 from patients with chronic hypertension, 38 from gestational hypertension, 152 from women who later developed pre-eclampsia, 88 from pre-existing hypertension with pre-eclampsia, 12 with other hypertensive disease and 78 from women with intrauterine growth restriction. From genetics (Barantke *et al* 2008) we considered measurements from 367 subjects with an age of 10 to 88 years (45.0 ± 16.3 years), 157 were male (43%). From cardiology (Boyé *et al* 2011) we used the measurements of 75 patients with chronic cardiac diseases referred for primary preventive implantable cardioverter-defibrillator implantation following Multicenter Automatic Defibrillator Implantation Trial study criteria, mean age 70.9 ± 10.1 years, body mass index 27.0 ± 3.5 . From Retzlaff *et al* (2009) 302 measurements from patients before and after aortic (AV) or mitral valve (MV) surgery were included for analysis. The mean age of the AV patients and MV patients was 62 ± 13 years and 59 ± 2 years, respectively. From Retzlaff *et al* (2011) 169 measurements from 58 consecutive patients undergoing either trans-catheter aortic valve implantation (TAVI) or surgical aortic valve replacement (SAVR) with the heart-lung machine and being in stable sinus rhythm were enrolled. Thirty-four of them underwent SAVR and 24 of them TAVI, 28 male, mean age 64.6 ± 13.8 in the SAVR group and 80.5 ± 7.3 in TAVI.

All these studies contained measurements that were performed under supine resting position for 30 min using a Task Force Monitor (CNSystems, Graz) or a PortaPres device (Finapres Medical Systems, Enschede). In total we gathered 1828 time series containing the beat-to-beat values of heart rate (HR) as well as systolic blood pressure (SBP). Exclusion criteria were atrial fibrillation, pacemaker activity, technical artefacts, as well as ectopy time greater than 10%, reducing the number of time series to 1576-careful visual inspection for further technical and physiological artifacts reduced the subjects for reanalysis to 1475.

3. Methods

Initially, BRS was measured and defined by injecting vasoconstrictive agents to increase blood pressure, thus reflexly increasing the beat-to-beat intervals via the baroreceptors. Later, attempts started to assess BRS noninvasively, most frequently from spontaneous HRV and BPV obtained from a continuous finger pressure measurement (Rothlisberger *et al* 2003). The underlying idea is that there is always some spontaneous BPV, for example due to respiration as well as changes which are observed as Mayer waves (Karemaker and DeBoer 2017), which may enable to estimate the BRS. In this paper, SME was calculated via the standard sequence method (Bertinieri *et al* 1985), quantifying both tachycardic as well as bradycardic sequences. Tachycardic sequences are defined as three consecutive heartbeats with decreases of systolic blood pressure simultaneously leading to decreases of beat-to-beat intervals (i.e. tachycardic event). Bradycardic sequences, correspondingly, are defined as three consecutive heartbeats with increases of systolic blood pressure simultaneously leading to successive increases of beat-to-beat intervals (i.e. bradycardic reaction). Finally, we calculated the overall SME as suggested by Porta *et al* (2013): SME as a BRS estimate is defined as the change in beat-to-beat interval in milliseconds per unit change in blood pressure averaged over all valid baroreflex sequences. A valid baroreflex sequence must satisfy: (i) three beats length, (ii) 5 ms and 1 mmHg minimum beat-to-beat changes in HR and SBP respectively and (iii) a correlation coefficient of at least 0.85. The delay with higher correlation coefficient between arterial blood pressure and RR sequences was selected on an index basis either $\tau = 0$ or $\tau = 1$ as suggested by Karemaker and DeBoer (2017). In addition, at least five valid sequences are required for SME.

Different parameters from the time domain were calculated to quantify short term HRV and BPV (Task Force 1996) of the filtered beat-to-beat intervals: meanNN, the mean value; sdNN, the standard deviation; RMSSD, the root mean square of successive difference; meanBP, the mean systolic blood pressure value; sdBP, the standard deviation of the systolic blood pressure and RMSSD_{SBP}, the root mean square of successive difference of the systolic blood pressure. Analogous to the SME definition, RMSSD_{RATIO} was calculated as RMSSD divided by RMSSD_{SBP}. Additionally, Pearson correlation coefficients between SME and these measures were quantified.



For humans, blood pressure and heart periods fluctuate at respiratory and other frequencies and are driven by autonomic nervous system activity, according to Karemaker (2009). They provide optimal adaptation of the cardiorespiratory system to internal and environmental factors. There is a controversial discussion if these fluctuations, whether central or peripheral, are reflex driven or not (Karemaker 2009, Eckberg 2009).

To test whether SME does quantify causal relationships between heart rate and blood pressure, and thusly spontaneous BRS, we performed the following surrogate analyses:

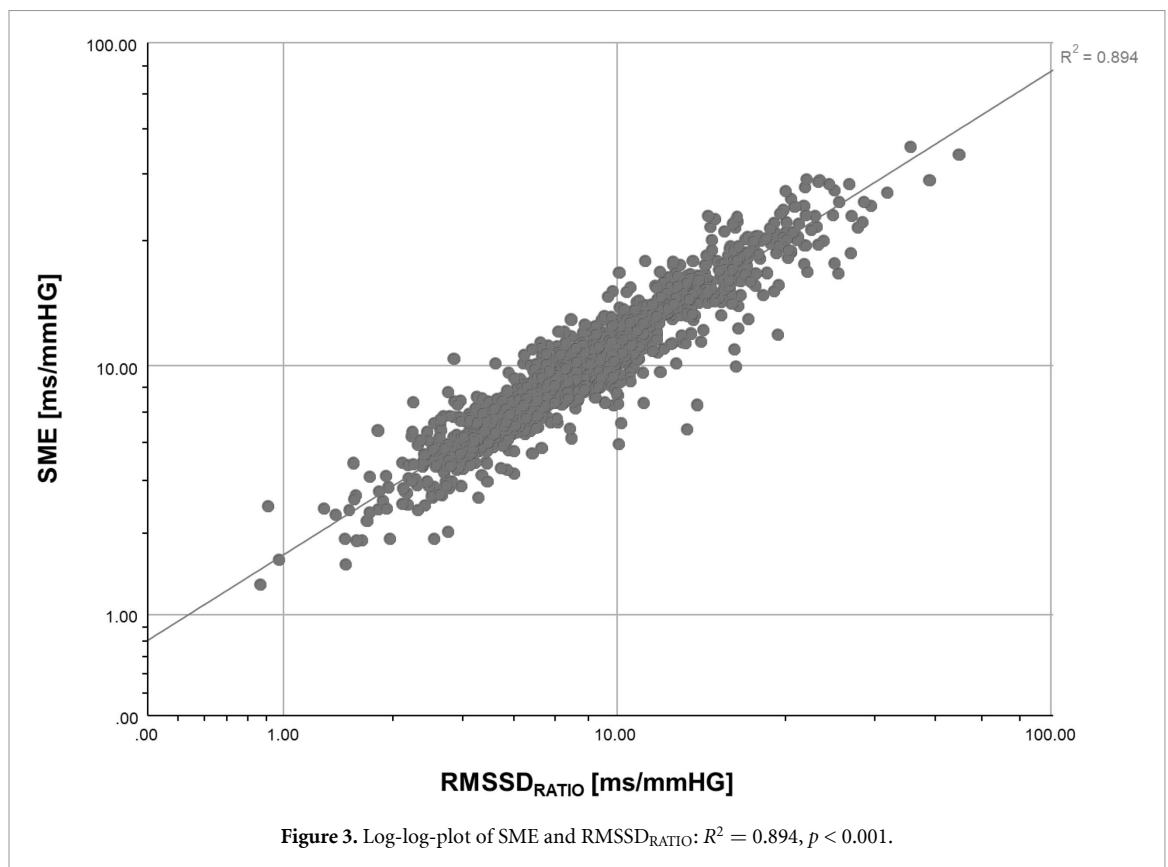
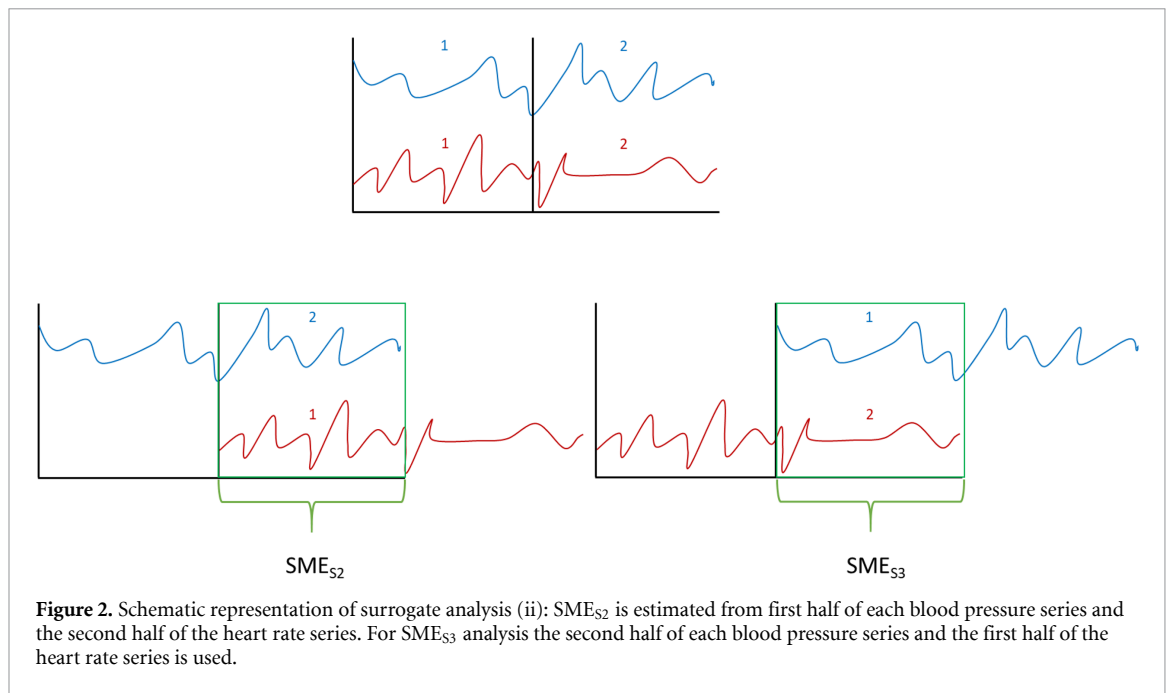
- (i) For all time-series the systolic blood pressure values were reversed, i.e. the first blood pressure value is now the last, the second now the second last etc. This surrogate data obviously has the same distribution as the original data, since the values of each point are the same but now just in a different time position. However, now there can be no causal relationship between heart rate and blood pressure (cf. figure 1, SME_{S1}).
- (ii) All time-series were bisected into two time-series of equal length of 15 min. First, SME and variability parameters were calculated for all time-series for intervals of 15 min. Second, the first half of each heart rate series was assigned to the second half of the blood pressure series. This surrogate data does not guarantee to have the same distribution as the original data, however, there cannot be any direct short-term causal relationship, because of the temporal disconnect between heart rate and blood pressure data (cf. figure 2, SME_{S2} and SME_{S3}).
- (iii) For all time-series the beat-to-beat-intervals were shuffled using the IAFFT approach (Schreiber and Schmitz 1996). In this way, again, there can be no causal relationship between heart rate and blood pressure (SME_{S4}).

Our hypothesis for the surrogate tests is ‘SME does quantify causal relationships between heart rate and blood pressure’.

4. Results

The set of reanalyzed time series ($n = 1475$) contained 14 (0.9%) cases, where no valid sequences were found and therefore SME could not be calculated. The highest correlation coefficient between SME and short-term variability parameters was found for RMSSD ($r = 0.85$, $p < 0.001$). The correlation coefficients r between SME and further HRV and BPV parameters are given in table 2. The highest correlation coefficient between SME and all others was found for $RMSSD_{RATIO}$ ($r = 0.93$, $p < 0.001$, cf. figure 3).

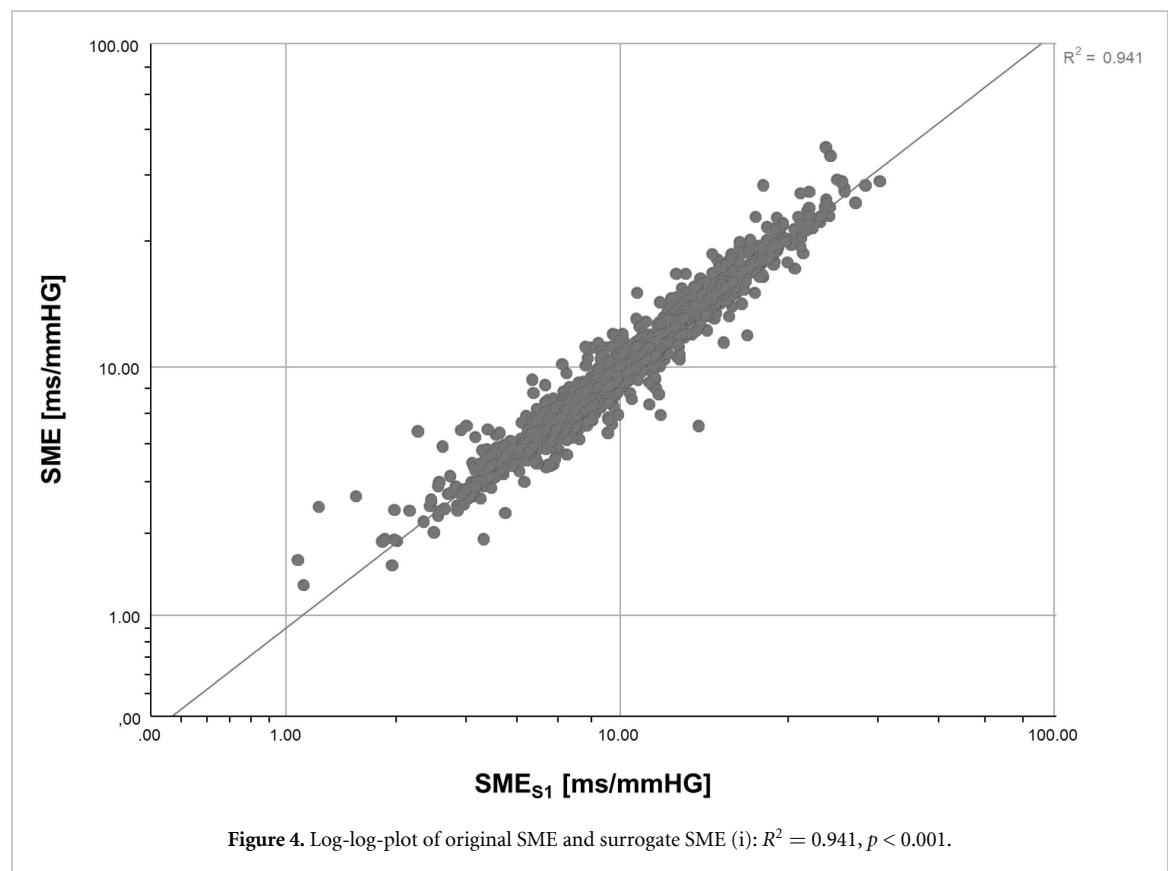
Surrogate analysis (i) contained 9 (0.6%) cases, where no valid sequences were found and therefore SME_{S1} could not be calculated. The correlation coefficient in surrogate analysis (i) between SME_{S1} and $RMSSD_{HRV}$ was $r = 0.85$, $p < 0.001$, i.e. reversing one time series does not affect the results of SME. Moreover, the correlation coefficient between SME_{S1} and $RMSSD_{RATIO}$ was equally high with $r = 0.91$, $p < 0.001$. Finally, the correlation coefficient between original and surrogate SME_{S1} was extreme high with $r = 0.97$, $p < 0.001$ (cf. table 2, figure 4).



In surrogate analysis (ii) the original 15 min time series contained 35 (2.4%) cases, where no valid sequences were found and therefore SME_{S2} could not be calculated. For the artificial assigned surrogates this number was 25 (1.6%). The mean SME for the original series was 11.1 ± 6.0 , whereas for the surrogate SME_{S2} it was 11.1 ± 5.6 ($p = \text{n.s.}$, paired t-test, SME against SME_{S2}), the correlation between them was 0.93, $p < 0.001$ (cf. table 2). The only difference between the original and the surrogate, was for the ratio of found sequences to the number of overall possible ones (16.2% vs. 10.0%, $p < 0.001$). Moreover, the correlation coefficient between surrogate SME_{S2} and the original $RMSSD_{RATIO}$ again was equally high with $r = 0.92$, $p < 0.001$. Surrogate analysis (ii) was performed a second time: SME_{S3} , where the first half of each blood pressure series were assigned to the second half of the heart rate series and revealed similar results (cf. table 2).

Table 2. Basic statistics for all parameters from the whole analysis (Mean \pm Sd: mean value \pm standard deviation) and the correlation coefficient r to SME (R to SME, $p < 0.001$ for all coefficients).

	Mean \pm Sd	R to SME
SME [ms/mmHg]	11.1 \pm 6	1
SME _{S1} [ms/mmHg]	11.2 \pm 5.4	0.97
SME _{S2} [ms/mmHg]	11.1 \pm 5.6	0.93
SME _{S3} [ms/mmHg]	11.3 \pm 5.6	0.94
SME _{S4} [ms/mmHg]	10.9 \pm 5.2	0.95
meanNN [ms]	761 \pm 146	0.5
meanBP [mmHg]	129 \pm 22.4	−0.23
sdNN [ms]	42.5 \pm 18.6	0.69
sdBP [mmHg]	8.1 \pm 2.9	−0.2
RMSSD [ms]	25.6 \pm 14.7	0.85
RMSSD _{SBP} [mmHg]	2.9 \pm 1	−0.23
RMSSD _{RATIO} [ms/mmHg]	9.5 \pm 6.1	0.93



Surrogate analysis (iii) contained 5 (0.3%) cases, where no valid sequences were found and therefore SME_{S4} could not be calculated. The correlation coefficient between SME_{S4} and RMSSD_{HRV} was $r = 0.87$, $p < 0.001$. Moreover, the correlation coefficient between SME_{S4} and RMSSD_{RATIO} was equally high with $r = 0.91$, $p < 0.001$. Finally, the correlation coefficient between original and surrogate SME_{S4} again was extreme high with $r = 0.95$, $p < 0.001$ (cf. table 2).

In table 3 the basic statistics for all parameters for all sub-studies are given, highest SME values were found in the genetics study with no organic heart diseases. The values of SME and the corresponding surrogate SME (SME_{S1}, SME_{S2}, SME_{S3}, SME_{S4}) do not differ significantly in each sub-study.

In table 4 different correlation coefficients r for all sub-studies are given. The correlation between SME (SME_{S1}, SME_{S2}, SME_{S3}, SME_{S4}) and RMSSD is high, the correlation to RMSSD_{RATIO} mostly much higher. To address concerns for bias due to inclusion of multiple measurements per subjects, we reran the analysis on a reduced data set with only the first measurement per subject ($n = 749$) and got similar correlations (SME vs. RMSSD: 0.85, SME vs. RMSSD_{RATIO}: 0.92, SME_{S1} vs. RMSSD: 0.86, SME_{S1} vs. RMSSD_{RATIO}: 0.88, SME vs. SME_{S1}: 0.97). In summary, matching time series with different time bases does not affect the results of SME, which shows that SME has a potentially large methodological bias as an estimate for the spontaneous BRS.

Table 3. Basic statistics for all parameters for all sub-studies (mean value \pm standard deviation).

	Obstetrics	Genetics	Cardiology	Surgery I	Surgery II
SME	10.4 \pm 4.5	12.8 \pm 7.6	11 \pm 4.3	9.1 \pm 5.1	9.3 \pm 5.1
SME _{S1}	10.7 \pm 4.1	12.6 \pm 7.2	11 \pm 4.2	9.3 \pm 5.1	9.5 \pm 5
SME _{S2}	10.5 \pm 4.2	12.8 \pm 7.4	11.1 \pm 4.2	9.3 \pm 5.9	9.7 \pm 5.6
SME _{S3}	10.9 \pm 4.6	12.3 \pm 7.1	10.7 \pm 4.3	9.3 \pm 5.3	9.6 \pm 5.2
SME _{S4}	10.6 \pm 4.2	12.1 \pm 6.4	10.1 \pm 3.8	8.9 \pm 5.1	9.0 \pm 4.4
meanNN	700 \pm 102	829 \pm 137	971 \pm 186	847 \pm 145	860 \pm 127
meanBP	132 \pm 24	129 \pm 18	117 \pm 15	113 \pm 18	122 \pm 16
sdNN	43 \pm 16	47 \pm 20	36.9 \pm 15.5	28 \pm 16	29 \pm 16
sdBP	8.7 \pm 2.5	7 \pm 2.2	5.2 \pm 1.6	7.4 \pm 4	7.7 \pm 4.4
RMSSD	23.7 \pm 12.3	32.5 \pm 17	24.1 \pm 11.7	19 \pm 13.2	18.4 \pm 11
RMSSD _{SBP}	2.9 \pm 0.7	3.3 \pm 1.1	2.1 \pm 0.8	2.7 \pm 1.4	2.5 \pm 1.4
RMSSD _{RATIO}	8.5 \pm 4.1	11 \pm 6.5	12 \pm 5.5	8.1 \pm 6.2	9 \pm 6.5

Table 4. Different correlation coefficients r for all sub-studies ($p < 0.001$ for all intergroup coefficients).

	Obstetrics	Genetics	Cardiology	Surgery I	Surgery II
SME vs. RMSSD	0.85	0.87	0.84	0.79	0.72
SME vs. RMSSD _{RATIO}	0.97	0.95	0.8	0.91	0.92
SME _{S1} vs. RMSSD	0.85	0.87	0.81	0.76	0.74
SME _{S1} vs. RMSSD _{RATIO}	0.97	0.95	0.8	0.9	0.88
SME _{S2} vs. RMSSD	0.77	0.83	0.83	0.79	0.81
SME _{S2} vs. RMSSD _{RATIO}	0.91	0.91	0.8	0.86	0.8
SME _{S3} vs. RMSSD	0.84	0.84	0.73	0.69	0.67
SME _{S3} vs. RMSSD _{RATIO}	0.93	0.93	0.81	0.88	0.85
SME _{S4} vs. RMSSD	0.87	0.89	0.89	0.87	0.82
SME _{S4} vs. RMSSD _{RATIO}	0.97	0.95	0.81	0.92	0.9

The hypothesis that SME quantifies causal relationships between heart rate and blood pressure must be rejected.

5. Discussion

In this letter, we tested the hypothesis: ‘SME does quantify causal relationships between heart rate and blood pressure’. To test this hypothesis, we rearranged the time basis of one of the time series and this surrogation did not affect the results of the SME. In all surrogates there can be no causal relationship between heart rate and blood pressure by construction. However, SME is unchanged in the absence of causal relations, thus it cannot distinguish between causal and spurious sequences. Therefore, the hypothesis that SME quantifies causal relationships between heart rate and blood pressure must be rejected.

Our study suggests that the origin of the information underlying the results of the SME, which is retained in the surrogates, can be mostly found in the short term HRV, as quantified by RMSSD under resting conditions. To explain most of the residue of this univariate model, the simple bivariate model RMSSD_{RATIO} suffices, which does not rely upon any causal interactions.

In contrast, La Rovere *et al* (1998) could show that low values of either long-term HRV (SDNN < 70 ms) or pharmacologically determined baroreflex sensitivity (pBRS < 3 ms per mmHg) independently carry a significant risk of cardiac mortality after myocardial infarction. This indicates a difference between SME estimates from a resting state and a more fully exhaustive pBRS, which in the latter relates not only to respiratory induced fluctuations but also to carotid distensibility (La Rovere *et al* 2011). We suspect that the SME is unreliable in cases of relative shallow breathing. In this case we only have small respiratory induced blood pressure variations leading to only small baroreceptor activations and thus to a low HRV and consequently SME. However, in such cases the baroreflex may actually be fully functional and its sensitivity in the normal range; they only cannot be reliably quantified via the SME. In our data base 215 subjects (13.9%) show low blood pressure variability (RMSSD_{SBP} is less than 2 mmHg) indicating only small respiratory induced oscillations. This low variability could lead to an insufficient basis for reliable baroreflex sensitivity estimation (cf. baroreflex function curve).

Lipman *et al* (2003), indeed observed the correlation between resting state SME and pBRS to be only $r = 0.5$. An increase of SME values, while subjects breathe deeply, lead Tzeng *et al* (2009) to test this observation in a systematic fashion. The hypothesis was that controlled slow breathing, which induces blood

pressure fluctuations greater than 4 mmHg, enhances the cardiovascular baroreflex gain in young healthy volunteers. The baroreflex gain was examined using the classical pBRS as well as the non-invasive SME methods. Compared to normal breathing, slow breathing was associated with a significant increase in the SME-index, whereas pBRS was unaltered. The SME values at slow breathing are higher than the pBRS ones in the study, possibly overestimating the gain. However, Arica *et al* (2011) demonstrated that the phenylephrine injection using pBRS may be predicted from non-pharmacological indices acquired during deep breathing. From both studies we derive the opinion that autonomic testing should allow a reliable, non-invasive, non-pharmacological driven quantification of the baroreflex gain.

Summarizing our findings, we can state: For short measurements under resting conditions RMSSD_{RATIO} carries similar vagally mediated information as SME, however the latter has a potentially large methodological bias as an estimate for the baroreflex sensitivity. Moreover, it must be tested whether further existing causal and non-causal methods for BRS assessment (Pagani *et al* 1988, Porta *et al* 2000, Faes *et al* 2013) also have such methodological bias for baroreflex sensitivity estimation. Further investigations will show whether certain autonomic testing procedures (deep breathing, orthostatic test, carotid occlusion, neck suction...) can serve as a basis for noninvasive evaluations of baroreflex sensitivity, which is currently probably still best quantified by pBRS, regardless of state of immediate autonomic excitation.

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